Attachment 1 – Critical Path Opportunity-related Comments

Process-related

- We would like to see additional efforts by the Agency in areas such as standardizing review approaches within and across Divisions, and putting more emphasis on the predictability of first round approvals.

- The critical path initiative provides an opportunity to improve the development and review of new technologies and therapies, particularly those that cross FDA Centers and therapeutic Divisions. There is a need to develop clear processes for gaining Agency agreement on the path forward with such opportunities.

- It is obvious that the increased cost in medical product development is driven largely by clinical requirements. This initiative focuses on tools for the prediction of clinical safety/effectiveness as a way to avoid clinical failures. We agree with this concept, but also see this as an opportunity to target new ways in which clinical trials can be done more efficiently, e.g., the use of Bayesian statistics in the Center for Devices and Radiologic Health (CDRH) that has proven to be less costly, more efficient, and more timely.

- We interpret the Critical Path to begin from selection of a molecule/device for development through to launch. There are opportunities for improvement all along this Path.

Science-related

- The 1997 Food and Drug Administration Modernization act stipulated that evidence of effectiveness could be based upon "data from one adequate and well-controlled investigation and confirmatory evidence". Such confirmatory evidence could be based upon "convincing evidence of the pharmacologic mechanism of the clinical effect of a drug" (Peck, CC. et al, Clinical Pharmacology and Therapeutics 73, p.481-490; 2003.). However, in most incidences, health authorities including the FDA and European agencies have continued to require two independent pivotal trials. If methods involving biomarkers, and PK/PD modeling are further instituted, one would hope that these would be used as the confirmatory evidence for one positive trial, and not simply added to the burden of two positive trials (reference is made to the Agency's definition of valid scientific evidence under 21 CFR 860.7).

  FDA has accomplished a great deal in its efforts to help industry make new oncology products available, and has had real success in creatively using postmarketing requirements, surrogate markers, etc., to accelerate development and availability. While the risk/benefit decisions in oncologic

diseases may seem more compelling, this same approach could be used in other serious degenerative disease states to create opportunities to encourage and accelerate development of much needed therapies.

An example of a degenerative disease state that affects increasingly large numbers of patients would be Congestive Heart Failure (CHF). There is not consensus in the medical community about how to define CHF, how to treat it nor how to study it. There have been very few new products in this therapeutic area over the last several decades, and the burden on the patient and the health care system is very heavy. CMS has initiated pilot programs on disease management to work with the medical community, hospitals, and, to a lesser extent, industry, to investigate better treatment algorithms and discover ways to reduce patient suffering and health care costs. FDA can play a valuable role in such efforts, due to its vast knowledge base and medical/scientific expertise. In this context, the Agency and industry can examine the best means to use all existing public data. Historical controls, registries, and other published data might be used to create a complete data set in line with the provisions from FDAMA. Full and fair discussion of all data and information available could help move the field to new consensus on definitions and treatment for CHF.

We clearly support the use of biomarkers and surrogate endpoints for effectiveness to drive rapid clinical development.

?? A more streamlined development path for the innovator company can, in many cases, be applied to alternative indications or new formulations for already approved medical products.

Additional Points Not Currently Addressed in Report

?? Implementation will require extensive collaboration across health authorities, industry, and the scientific community. While the FDA is in a good position to lead in the development of a national *and an international* Critical Path Opportunities List, it cannot lead all aspects of this enormous initiative. Multiple work streams will be necessary, offering opportunities for many to make significant contributions. We support the establishment of a multidisciplinary steering committee for the Critical Path Initiative (FDA across Centers, industry, academia), with specific objectives, milestones, follow-up activities, and accountability to be identified.

?? It is unclear how the new product development toolkit can help encourage sponsors concentrate their efforts not only on products with potentially high market return, but also on products targeted for less common diseases,

prevention indications, or diseases that predominantly afflict the poor.

?? We need to have talented personnel working and retained at FDA to help in this Critical Path Initiative. CDRH has a successful university student co-op program run by Susan A. Homire, Senior Science Advisor. She evaluates the gaps in expertise in the Center in addition to technology trends that will likely appear in future applications for review, and strategically targets expertise from universities accordingly. We recommend that this program be expanded across other Centers.

?? The Agency needs a standing process to educate reviewers on new procedures and new technologies.

?? The Agency should address needs for clinical data/clinical studies and develop distinctions between such things as tool devices, therapeutic devices, and special class of tools (e.g., for In Vitro Diagnostics [IVDs]). An example of a "tool" claim for IVDs would be claims unrelated to clinical effect, that is, a claim for a test to read presence or levels of a particular analyte, with no further discussion of clinical relevance of the analyte.